J. Braz. Chem. Soc., Vol. 21, No. 9, 1656-1663, 2010.
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0103 - 5053 $6.00+0.00

Article

Succinic Acid Dihydrazide: a Convenient *N,N*-Double Block for the Synthesis of Symmetrical and non-Symmetrical Succinyl-bis[5-trifluoro(chloro)methyl-1*H*-pyrazoles]

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Este trabalho apresenta a síntese regiosseletiva de séries de bis-2-pirazolinas e bis-1*H*-pirazóis succinil intercalados inéditas, denominadas 1,4-bis[5-(trifluormetil)-5-hidróxi-4,5-diidro-1*H*-pirazol-1-il]butano-1,4-dionas (46-88%), o respectivo sistema desidratado (60-78%), 1-[5-(trifluormetil)-5-hidróxi-4,5-diidro-1*H*-pirazol-1-il]-4-oxabutano hidrazidas (52-81%) e 2-pyrazolinas derivadas não simétricas, como 1-[5-(trifluormetil)-5-hidróxi-4,5-diidro-1*H*-pirazol-1-il)-4-(5-(triclorometil)-5-hidróxi-4,5-diidro-1*H*-pirazol-1-il]butano-1,4-dionas (75-91%). Todos os bis-pirazóis succinil substituídos foram obtidos a partir de reações de ciclocondensação de 4-alcóxi-1,1,1-trialo-3-alquen-2-onas 4-substituídas (4-substituinte = H, Me, fenil, 4-FC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 1-naftil and 2-furil), com dihidrazida succínica, em etanol como solvente, sob condições reacionais convencionais controladas.

This paper describes the conventional regioselective synthesis of a series of new succinyl spacer bis-(3,5-substituted 2-pyrazolines and 1*H*-pyrazoles), namely; 1,4-bis[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (46-88%) and the respective dehydrated system (60-78%), new 1-[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutane hydrazides (52-81%) and the non-symmetrical 2-pyrazolines derivatives thereof as 1-[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (75-91%). All succinyl substituted bispyrazoles were obtained from the cyclocondensation reactions of 4-substituted 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones, where the 4-substituents are H, Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 1-naphthyl and 2-furyl, with succinic acid dihydrazide in ethanol as solvent under controlled reaction conditions.

Keywords: succinic acid dihydrazide, vinyl ketones, 2-pyrazolines, bis-pyrazoles, butanediones

Introduction

Bis-pyrazolyl ketones and similar chemical structures have been most commonly synthesized by substitution reactions involving phosgene, esters or alkyl- and acyl-dihalides with 1*H*-pyrazoles.[1-7] However, this synthetic procedure is efficient for this synthesis starting only from symmetric substituted or non-substituted 1*H*-pyrazoles because non-symmetric 3- or 5-substituted 1*H*-pyrazoles existing in two tautomeric structures, in solution, and their *N*[1]-substitution reactions lead to three possible bis-pyrazolyl spacer isomers.

Moreover, bis-pyrazolyl containing acyl spacer groups are rare in the literature and new synthetic routes to obtain these compounds and studies of their potential as pharmaceuticals and agrochemicals, such as herbicidal agents, have been relatively little explored.[8-11]

A review of the literature showed few publications about the construction of a succinyl spacer bis-(3,5-substituted 1*H*-pyrazoles) system. In 1961, according to a US patent, Wright[8] reported the systematic synthesis and a biological activity study of a series of bis-(4-nitropyrazol-1-yl) spacer compounds, where the linker moiety was an aliphatic hydrocarbon chain [-$(CH_2)_n$-] containing 1 to 12 carbon atoms, saturated or unsaturated, and substituted by one or more lower alkyl (not more than 4 carbon atoms) or

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hydroxyl groups. In the same patent, diacyl group spacers [-CO-$(CH_2)_n$-CO-] with *n* being an integer from 1 to 12, or an ether group of the formula [-$(CH_2)_x$-O-$(CH_2)_y$-], where *x* and *y* are identical or different integers from 1 to 10; or even a divalent cycloalkyl group such as 1,4-cyclohexylene, were synthesized and biologically tested. These new bis-pyrazolyl compounds showed useful activity as antiprotozoal agents, especially in the treatment of trichomoniasis (*e.g.*, that caused by *T. vaginalis*). The 1,7-di-(4-nitropyrazol-1-yl) *n*-heptane and their respective *n*-pentane analogue were of outstanding activity and low toxicity. Specifically, only 1,1'-succinylbis(3,5-dimethyl-4-nitropyrazole) and the non-substituted 1,1'-succinyl bis-(4-nitropyrazole) were prepared using the appropriate 1*H*-pyrazole and succinyl chloride. In 2005, Shi *et al*.[12] reported the synthesis of *N,N'*-butanedioylbis(5-ferrocenyl-3-methyl-1*H*-pyrazole) from the reaction of ferrocenoylacetone and succinic acid dihydrazide. In the same year, Al-Talib *et al*.[13] reported that the reaction of oxalic, malonic and succinic acid dihydrazide with 2,4-pentanedione gave smoothly the corresponding oxalyl-, malonyl- and succinyl-*N,N'*-bis(3,5-dimethyl-1*H*-pyrazole). It is also important to mention that aroyl and heteroaroyl spacer bispyrazoles have been synthesized employing 1,3-dicarbonyl compounds or derivatives thereof and, for example, isophthalic acid dihydrazide[14] or 1,3,4-thiadiazole-2,5-dithioglycolic acid dihydrazide,[15] respectively.

More recently, pyrazolylcarbohydrazides have been cited as new and promising antitumor drugs and have been synthesized and studied mostly as a potential lung cancer cell growth suppressant. In 2007,[16] a series of 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives was synthesized and their effects on A549 cell growth and apoptosis were evaluated. The structure-activity relationships and prediction of lipophilicity of the compounds were also studied. Later, in 2008,[17] a new series of 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives was synthesized. All of the 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives inhibited the growth of A549 cells in dosage- and time-dependent manners. Typically, any compounds induced A549 and H460 cells to autophagy, but did not inhibit the growth of human umbilical vein endothelial cells (HUVEC). Thus, one can see that not only the bis-(pyrazolyl) spacer compounds, but also the pyrazolylcarbohydrazide intermediates are important.

Recently, our laboratory reported the regioselective synthesis of seven examples of 3-(alkyl/aryl/heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazolyl-1-carbohydrazides (44-86%) and four examples of bis-(3-aryl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)methanones (73-89%) from cyclocondensation reactions of 4-substituted 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones, where the substituents were H, alkyl, aryl and heteroaryl with carbohydrazide, and symmetrical bis-pyrazolylmethanones were obtained, where the substituents at the 3 and 5 positions of the pyrazoles could be different from each other.[18] In the same work, bis-(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl) methanone was subjected to dehydration under various reaction conditions, but in all attempts the aromatized 1*H*-pyrazole was obtained with the simultaneous removal of the carbonyl function due to the cleavage of both C(O)–N bonds.

On the other hand, it is well-known that the introduction of a trifluoromethyl group into heterocyclic compounds may have a significant influence on their biological and physical properties and the simple replacement of a hydrogen atom by a fluorine atom is a strategy widely used in drug development to alter biological functions. The resulting change in the electron distribution of a molecule following this replacement can alter the pK_a, the dipole moments, and even the chemical reactivity and stability of neighboring functional groups. In terms of drug design, the employment of fluorinated molecules can be used to alter the rate of drug metabolism and thereby the production of a longer duration of action.[19]

The most convenient method to construct trifluoro and trichloromethylated heterocycles, including trihalomethyl substituted 2-pyrazolines and many pyrazoles, is to use fluorine- and chlorine-containing building blocks as starting reagents. Thus, 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trifluoro(chloro)alk-3-en-2-ones are versatile precursors for the heterocyclic synthesis and direct construction of this type of heterocycles.[20-23]

In this context and in an attempt to develop synthetic methods to obtain acyl spacer heterocycles and new fluorinated molecules, herein we report a practical and regioselective methodology for the preparation of a series of 1,4-bis(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)butane-1,4-diones (**2**) and the respective dehydrated bis-pyrazole systems (**3**), new 1-(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-oxobutane hydrazide intermediates (**4**) and the non-symmetrical 2-pyrazoline derivatives thereof as 1-(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)butane-1,4-diones (**5**) from the cyclocondensation reactions of 4-substituted 1,1,1-trifluoro(chloro)alk-3-en-2-ones (**1**) with succinic acid dihydrazide in ethanol as solvent under conventional and controlled reaction conditions (Schemes 1 and 2).

Results and Discussion

Since the 1970s, according to previous publications,[20-23] research groups have reported the systematic synthesis of 4-substituted 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones (**1**) from the trihaloacetylation reaction of the respective enolethers (**1a**, **1b**) or acetals (**1c**-**i**) with trifluoracetic anhydride or trichloroacetyl chloride, respectively.

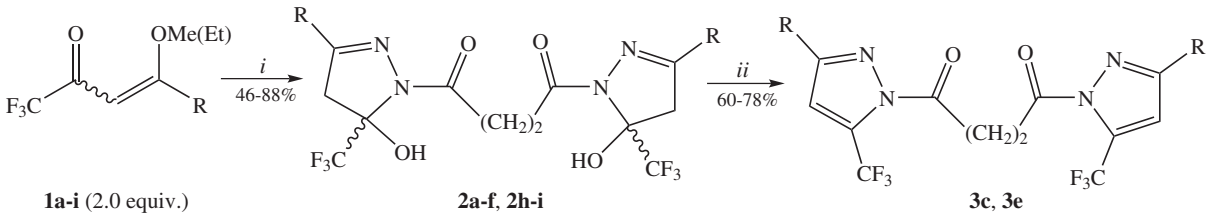
According to the literature,[8] 1,1'-succinyl-bis(3,5-dimethyl-4-nitropyrazole) and the non-substituted 1,1'-succinyl-bis(4-nitropyrazole) were prepared using the appropriate 1*H*-pyrazole and succinyl chloride in the presence of anhydrous sodium carbonate when the reactions were carried out in dry acetone as solvent for 20 h at 20 ºC, but no yields were reported.

In this work, we initially carried out the reaction of 4-methoxy-4-phenyl-1,1,1-trifluoro-3-alken-2-one (**1c**) with succinic acid dihydrazide in a 2:1 molar ratio, in ethanol as solvent at room temperature, however when monitored by TLC no reaction was observed. Subsequently, when the mixture was heated to reflux, after stirring for 6 h, TLC showed that the reaction proceeded smoothly and gave the product **2c** in 79% yield (Scheme 1). The most satisfactory results for the synthesis of the other compounds **2** were obtained from the reaction condition described above and were isolated as stable solids by recrystallization from ethanol.

Subsequently, after a review of the literature and attempting to obtain aromatic pyrazoles for further biological assays, we chose thionyl chloride/pyridine as the dehydration agent and report here the conditions required to accomplish the dehydration of two representative examples of compounds **2**, which present a hydroxyl- and a trifluoromethyl-group, a phenyl (for **2c**) or 4-fluorophenyl (for **2e**) and a succinyl 2-pyrazoline attached directly to the C-5, C-3 and N-1 atom of each pyrazoline ring, respectively (Scheme 1). Because of the relative difficulty to perform the dehydration reaction, due to the presence of a trifluoromethyl substituent and the carbonyl function at positions 5 and 1 of these two succinyl-bispyrazolines, **2c** and **2e** were dehydrated to give the respective 3-aryl-substituted 1,4-bis(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)butane-1,4-diones **3c** and **3e** in 78 and 60% yields, only by stirring the mixtures of **2c** or **2e**, thionyl chloride and pyridine at 80 ºC for about 1 h in benzene as solvent, according to similar procedures described in the literature.[24]

Motivated by the importance of some pyrazolylcarbohydrazides already described in the literature,[12,13] we attempted to synthesize some examples of new 1-(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-oxobutane hydrazides (**4**). We investigated this reaction employing 4-substituted 4-methoxy-1,1,1-trifluorobut-3-en-2-ones with two substituents with opposite electronic effects (4-methoxyphenyl and 4-nitrophenyl) and the neutral substituent 4-phenyl. Initially, we carried out the reaction of 4-methoxy-4-phenyl-1,1,1-trifluorobut-3-en-2-one (**1c**) with succinic acid dihydrazide in a 1:1 molar ratio in ethanol as solvent at room temperature from 4 to 24 h, however when monitored by TLC no reaction was observed and the starting materials were recovered. Surprisingly, when the mixture was heated to 50-55 ºC, after stirring for 3 h, TLC showed that the reaction proceeded smoothly and gave product **4c** in 81% yield (Scheme 2). The most satisfactory results for the synthesis of the other compounds **4** were obtained from the reaction condition described above and the compounds were isolated as stable white powders after the reaction time by simple filtration under reduced pressure in 52-81% yields.

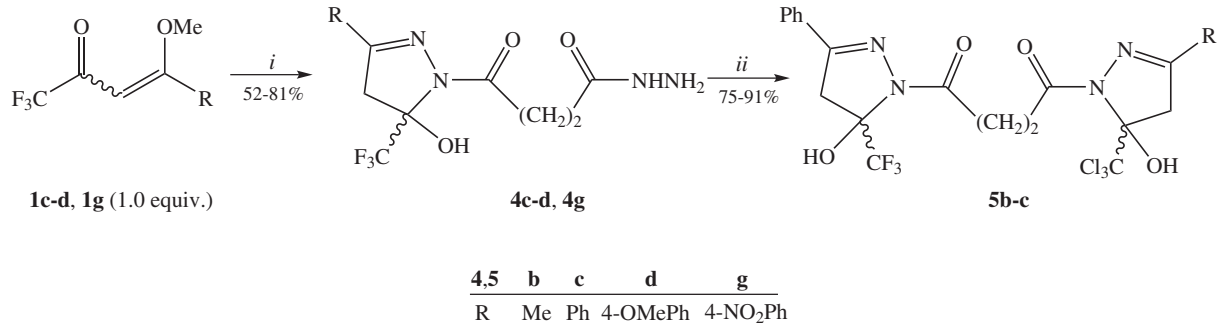
Finally, aiming to obtain examples of non-symmetrical succinyl spacer bis-pyrazoles, the reaction of 1-(3-phenyl-5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-oxobutane hydrazides **4c** with two trichlorometylated vinyl ketones (4-methoxy-1,1,1-trichloropent-3-en-2-one and 4-methoxy-4-phenyl-1,1,1-trichlorobut-3-en-2-one) was performed. In these cases, the desired products **5b** and **5c** were isolated in 91 and 75% yields, respectively,



1a-i (2.0 equiv.) **2a-f**, **2h-i** **3c**, **3e**

1-3	a	b	c	d	e	f	g	h	i
R	H	Me	Ph	4-OMePh	4-FPh	4-ClPh	4-NO_2Ph	2-Naphthyl	2-Furyl

Scheme 1. Reagents and conditions: (*i*) $(NH_2NHCOCH_2)_2$ (1.0 equiv.), EtOH, 5-10 h, 80 ºC; (*ii*) $SOCl_2$, pyridine, benzene, 1 h, 0-80 ºC.



Scheme 2. Reagents and conditions: (*i*) $(NH_2NHCOCH_2)_2$ (1.0 equiv.), EtOH, 4 h, 0-50 ºC; (*ii*) $CCl_3C(O)CH=C(OMe)R$ (1.0 equiv.), EtOH, 16 h, 50 ºC.

showing an interesting and promising employment of pyrazolyl substituted succinic acid hydrazides such as **4** (Scheme 2). Compounds **5** were obtained when the reactions of pure **4c** and 4-methoxy-1,1,1-trichloroalk-3-en-2-ones were carried out in a molar ratio of 1:1 at 50 ºC for about 16 h also in ethanol as solvent. A complex mixture of products was obtained when the reactions were carried out under refluxing ethanol for 1 to 2 h.

The structures of 1,4-bis[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (**2a**-**f**, **2h**-**i**) were deduced from NMR experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory.[18,22,23] Compounds **2** showed the ^{1}H NMR chemical shifts in DMSO-d_6 of the hydroxy protons in the range of δ 8.04 ppm and the four methylene protons (H4) are shown as a typical AB system as two doublets, in which, one of them is on average at δ 3.79 and the other at δ 3.44 ppm, with a geminal coupling constant of 19-20 Hz. Due to the symmetry of compounds **2**, the four ethylene protons (succinyl moiety) appeared as one singlet peak on average at 3.06 ppm. The ^{13}C{^{1}H}NMR spectra exhibited only one set of peaks, despite the fact that two stereogenic carbons are present in each molecule. The succinyl derivatives **2** also presented the typical ^{13}C NMR chemical shifts of the both pyrazoline rings at δ 149.8 ppm (C3) and δ 45.2 ppm (C4). Due to the presence of the CF_3 group, both C5 carbons presented a characteristic quartet at δ 90.3 ppm with $^2J_{CF}$ 33 Hz. Also, both CF_3 groups showed a typical quartet at δ 123.4 ppm with $^1J_{CF}$ 285 Hz and the two carbonyl and ethylene carbons showed NMR signals in the range of δ 170.1 ppm and 29.3 ppm, respectively. All the signals are consistent with ^{1}H and ^{13}C NMR chemical shifts of the pyrazoline and the succinyl moiety for this symmetrical system.

The dehydrated compounds **3c** and **3f**, being symmetrical systems, presented one set of signals in both ^{1}H and ^{13}C NMR spectra and, in comparison with **2c** and **2f** showed typical chemical shifts of the pyrazole ring for both H-4 on average at 7.5 ppm as singlet peaks. The ^{13}C{^{1}H} NMR spectra exhibited chemical shifts, in DMSO-d_6, for both pyrazole ring carbons on average at 152.6 (C3), 111.7 (C4), 134.1 (C5, $^2J_{CF}$ 41) and 119.1 ppm (CF_3, $^1J_{CF}$ 268). Both carbonyl and ethylene carbons showed signals in the range of δ 169.8 ppm and 29.5 ppm, respectively.

For the pyrazolyl-succinic acid hydrazides (**4**), the OH, NH and NH_2 groups showed ^{1}H NMR chemical shifts in DMSO-d_6 in the range of δ 7.97 ppm, δ 8.97 ppm and δ 4.15 ppm, respectively. Now, due to the non-symmetry of compounds **4**, the four methylene protons of the succinyl moiety appeared as broad peaks on average at 3.07 and 2.24 ppm. As expected, the ^{13}C{^{1}H} NMR spectra exhibited only one peak for each carbon of the pyrazoline ring and the hydrazinosuccinyl moiety.

The unambiguous ^{1}H and ^{13}C NMR chemical shift assignments of non-symmetrical 1-[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]-4-[5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl]butane-1,4-diones (**5b**-**c**), in DMSO-d_6 as solvent, were made by comparison with NMR data of other trifluoro(chloro)methyl substituted 2-pyrazolines formerly obtained in our laboratory.[18,22,23] In contrast to compounds **2**, molecules **5** showed two sets of NMR signals. The chemical shifts of the four diasterotopic methylene protons (H4) appeared, as typical AB systems, as four doublets with a geminal coupling constant on average at 19 Hz. The hydroxy protons, as two singlets, are shown in the ^{1}H NMR spectra in the range of δ 7.72-8.05 and the four methylene protons of the succinyl moiety appeared as broad peaks on average at 3.09 ppm and 2.97 ppm. Compounds **5** also presented the typical ^{13}C{^{1}H}NMR spectra where the chemical shifts for non-symmetrical structures showed separate signals for each pyrazoline ring carbons. Also, due to the non-symmetry of **5b**-**c**, the two carbonyl carbon methylene groups of the succinyl moiety appeared as four peaks which is consistent with NMR chemical shift assignments when compared with compounds **2** and literature data for trichloromethyl substituted 2-pyrazolines.[23]

Conclusions

In conclusion, in this study we showed that the conventional cyclocondensation reaction between 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trifluoro(chloro)alk-3-en-2-ones and succinic acid dihydrazide under controlled reaction conditions is a useful, simple and convenient procedure to obtain new succinyl spacer bis-(3,5-substituted 2-pyrazolines and 1*H*-pyrazoles), namely 1,4-bis(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl) butane-1,4-diones (46-88%) and the respective dehydrated system (60-78%), new 4-(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-oxobutane hydrazides (52-81%) and the non-symmetrical 2-pyrazolines derivatives thereof as 1-(5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)butane-1,4-diones (75-91%).

Experimental

General procedures

Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in DMSO-d_6 for **2**-**5** using TMS as internal reference and all coupling constants (*J*) are given in Hertz (Hz). The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

*Synthesis of 1,4-bis[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-diones (**2a**-**f**, **2h**-**i**)*

A solution of 4-substituted 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones (**1a**-**f**, **1h**-**i**) (10 mmol), succinic acid dihydrazide (5 mmol), ethanol (20 mL) and distilled water (1 mL) was stirred at 80 ºC for 5-10 h. After the reaction time the solvent was evaporated to half by rotatory evaporator under reduced pressure. After cooling (≤ 8 ºC) for 1-2 days the compounds **2a**-**f**, **2h**-**i** were obtained pure directly by filtration, washed with cold ethanol and dried under vacuum apparatus.

*1,4-bis[5-(Trifluoromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2a**)*

Yield 46%, mp 160-161 ºC. ^{1}H NMR: δ 7.76 (s, 2H, 2OH), 7.21 (s, 2H, 2H-3), 3.40 (d, *J* 20, 2H, 2H-4,), 3.10 (d, *J* 20, 2H, 2H-4), 2.90 (s, 4H, 2CH_2). ^{13}C NMR: δ 170.3 (2C=O), 144.9 (2C-3), 122.8 (q, ^1J 285, 2CF_3), 88.9 (q, ^2J 34, 2C-5), 46.0 (2C-4), 29.3 (2CH_2). Anal. Calc. for $C_{12}H_{12}F_6N_4O_4$ (390.08): C, 36.93; H, 3.10; N, 14.36%. Found: C, 37.05; H, 3.01; N, 14.62%.

*1,4-bis[5-(Trifluoromethyl)-5-hydroxy-3-methyl-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2b**)*

Yield 57%, mp 141-142 ºC. ^{1}H NMR: δ 7.65 (s, 1H, OH), 7.62 (s, 1H, OH), 3.39 (d, *J* 19, 2H, 2H-4), 3.05 (d, *J* 19, 2H, 2H-4,), 2.84 (s, 4H, 2CH_2), 2.00 (s, 6H, 2CH_3). ^{13}C NMR: δ 169.9 (2C=O), 153.6 (2C-3), 123.3 (q, ^1J 285, 2CF_3), 90.3 (q, ^2J 33, 2C-5), 47.8 (2C-4), 29.3 (2CH_2), 15.2 (2CH_3). Anal. Calc. for $C_{14}H_{16}F_6N_4O_4$ (418.11): C, 40.20; H, 3.86; N, 13.39%. Found: C, 40.16; H, 3.92; N, 13.55%.

*1,4-bis[5-(Trifluoromethyl)-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2c**)*

Yield 79%, mp 265-266 ºC. ^{1}H NMR: δ 8.02 (s, 1H, OH), 8.00 (s, 1H, OH), 7.79-7.81 (m, 4H, 2Ar), 7.49 (s, 6H, 2Ar), 3.89 (d, *J* 19, 2H, 2H-4,), 3.55 (d, *J* 19, 2H, 2H-4), 3.07 (s, 4H, 2CH_2). ^{13}C NMR: δ 170.3 (2C=O), 151.4 (2C-3), 130.6, 130.8, 128.8, 126.5 (12C, 2Ar), 122.6 (q, ^1J 285, 2CF_3), 91.1 (q, ^2J 33, 2C-5), 44.4 (2C-4), 29.4 (2CH_2). Anal. Calc. for $C_{24}H_{20}F_6N_4O_4$ (542.14): C, 53.14; H, 3.72; N, 10.33%. Found: C, 53.63; H, 3.01; N, 10.11%.

*1,4-bis[5-(Trifluoromethyl)-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2d**)*

Yield 78%, mp 219-221 ºC. ^{1}H NMR: δ 7.92 (s, 1H, OH), 7.90 (s, 1H, OH), 7.73-7.75 (m, 4H, 2Ar), 7.03-7.04 (m, 4H, 2Ar), 3.82 (s, 6H, 2OCH_3), 3.83 (d, *J* 19, 2H, 2H-4), 3.51 (d, *J* 19, 2H, 2H-4), 3.19 (s, 4H, 2CH_2). ^{13}C NMR: δ 170.1 (2C=O), 161.1 (2C, 2Ar), 151.1 (2C-3), 131.8, 122.7, 114.2 (10C, 2Ar), 122.8 (q, ^1J 285, 2CF_3), 90.8 (q, ^2J 33, 2C-5), 55.3 (2OCH_3), 44.5 (2C-4), 29.3 (2CH_2). Anal. Calc. for $C_{26}H_{24}F_6N_4O_6$ (602.16): C, 51.83; H, 4.02; N, 9.30%. Found: C, 51.84; H, 3.91; N, 9.58%.

*1,4-bis[5-(Trifluoromethyl)-5-hydroxy-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2e**)*

Yield 74%, mp 219-220 ºC. ^{1}H NMR: δ 7.68-7.75 (m, 4H, Ar), 7.26 (s, 2H, 2OH), 7.09-7.17 (m, 4H, 2Ar), 3.70 (d, *J* 18, 2H, 2H-4,), 3.50 (d, *J* 18, 2H, 2H-4), 3.23 (s, 4H, 2CH_2). ^{13}C NMR: δ 170.0 (2C=O), 163.4 (d, ^1J 248, 2C-F, 2Ar), 150.3 (2C-3), 128.5, 126.5, 115.4 (10C, 2Ar), 91.0 (q, ^2J 33, 2C-5), 123.2 (q, ^1J 285, 2CF_3), 44.2 (2C-4), 29.2 (2CH_2). Anal. Calc. for $C_{24}H_{18}F_8N_4O_4$ (578.12): C, 49.84; H, 3.14; N, 9.69 %. Found: C, 49.59; H, 3.25; N, 9.89%.

*1,4-bis[3-(4-Chlorophenyl)-5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2f**)*

Yield 63%, mp 189-191 ºC. ^{1}H NMR: δ 8.03 (s, 1H, OH), 8.01 (s, 1H, OH), 7.81-7.83 (m, 4H, 2Ar), 7.54-7.56 (m, 4H, 2Ar), 3.89 (d, *J* 19, 2H, 2H-4), 3.55 (d, *J* 19, 2H, 2H-4), 3.07 (s, 4H, 2CH$_2$). ^{13}C NMR: δ 170.1 (C=O), 169.8 (C=O), 153.6 (2C, 2Ar), 150.4 (2C-3), 135.1, 129.1, 127.3 (10C, 2Ar), 123.1 (q, ^1J 285, 2CF$_3$), 90.6 (q, ^2J 33, 2C-5), 44.2 (2C-4), 29.3 (2CH$_2$). Anal. Calc. for $C_{24}H_{18}Cl_2F_6N_4O_4$ (610.06): C, 47.15; H, 2.97; N, 9.16 %. Found: C, 47.21; H, 3.01; N, 9.11%.

*1,4-bis[5-(Trifluoromethyl)-5-hydroxy-3-(1-naphthyl)-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2h**)*

Yield 84%, mp 224-226 ºC. ^{1}H NMR: δ 9.18 (s, 1H, OH), 9.14 (s, 1H, OH), 8.01-8.13 (m, 6H, 2Ar), 7.87-7.91 (m, 2H, 2Ar), 7.56-7.66 (m, 6H, 2Ar), 4.14 (d, *J* 19, 2H, 2H-4,), 3.80 (d, *J* 19, 2H, 2H-4,), 3.23 (s, 4H, 2CH$_2$). ^{13}C NMR: δ 170.1 (2C=O), 151.1 (2C-3), 133.4, 130.9, 129.5, 128.9, 128.5, 127.4, 126.2, 125.7, 124.8, 124.5 (20C, 2Ar), 126.7 (q, ^1J 286, 2CF$_3$), 89.9 (q, ^2J 34, 2C-5), 46.6 (2C-4), 29.5 (2CH$_2$). Anal. Calc. for $C_{32}H_{24}F_6N_4O_4$ (642.17): C, 59.82; H, 3.76; N, 8.72%. Found: C, 59.26; H, 3.91; N, 8.98%.

*1,4-bis[3-(Fur-2-yl)-5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**2i**)*

Yield 88%, mp 213-214 ºC. ^{1}H NMR: δ 8.10 (s, 1H, OH), 8.07 (s, 1H, OH), 7.91 (d, 2H, 2Fur), 7.07 (d, 2H, 2Fur), 6.68 (dd, 2H, 2Fur), 3.79 (d, *J* 19, 2H, 2H-4), 3.43 (d, *J* 19, 2H, 2H-4), 2.97 (s, 4H, 2CH$_2$). ^{13}C NMR: δ 170.0 (2C=O), 145.7 (2C-3), 145.2, 142.8, 114.4, 112.1 (8C, 2Fur), 122.6 (q, ^1J 286, 2CF$_3$), 90.1 (q, ^2J 33, 2C-5), 44.1 (2C-4), 29.3 (2CH$_2$). Anal. Calc. for $C_{20}H_{16}F_6N_4O_6$ (522.10): C, 45.99; H, 3.09; N, 10.73%. Found: C, 45.39; H, 3.44; N, 10.78%.

*Synthesis of 1,4-bis[5-(trifluoromethyl)-1H-pyrazol-1-yl] butane-1,4-diones (**3c, 3f**)*

General procedure

A solution of bis-pyrazoline butane-1,4-diones (**2c**, **2f**) (2.8 mmol) and pyridine (33.8 mmol, 3 mL) in 50 mL of benzene was cooled to 0 ºC and thionyl chloride (16.8 mmol, 1.22 mL) diluted in 25 mL of benzene was added dropwise over 10 min. The solution was stirred for an additional 30 min, during which time the temperature was allowed to rise to 20 ºC. The mixture was then heated under reflux (bath temperature 80 ºC) for 1 h and then filtered to remove the pyridine hydrochloride at room temperature. The solution was extracted twice with benzene (2 × 50 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure by rotatory evaporator left **3c**, **3f** as solid products which were purified by recrystallization from ethanol.

*1,4-bis[5-(Trifluoromethyl)-3-phenyl-1H-pyrazol-1-yl] butane-1,4-dione (**3c**)*

Yield 78%, mp 180-181 ºC. ^{1}H NMR: δ 7.86-7.88 (m, 4H, 2Ar), 7.45-7.47 (m, 6H, 2Ar), 7.21 (s, 2H, 2H-4), 3.79 (s, 4H, 2CH$_2$). ^{13}C NMR: δ 169.6 (2C=O), 153.4 (2C-3), 135.0 (q, ^2J 41, 2C-5), 130.4, 129.9, 128.9, 126.3 (12C, 2Ar), 119.3 (q, ^1J 269, 2CF$_3$), 111.2 (2C-4), 29.7 (2CH$_2$). Anal. Calc. for $C_{24}H_{16}F_6N_4O_2$ (506.12): C, 56.92; H, 3.18; N, 11.06%. Found: C, 56.98; H, 3.34; N, 10.92%.

*1,4-bis[5-(Trifluoromethyl)-3-(fluorophenyl)1H-pyrazol-1-yl]butane-1,4-dione (**3f**)*

Yield 60%, mp 189-190 ºC. ^{1}H NMR: δ 8.06-8.11 (m, 4H, 2Ar), 7.95 (s, 2H, 2H-4), 7.33-7.42 (m, 4H, 2Ar), 3.73 (s, 4H, 2CH$_2$). ^{13}C NMR: δ 170.1 (2C=O), 163.1 (d, ^1J 246, 2C-F, 2Ar), 151.8 (2C-3), 133.3 (q, ^2J 41, 2C-5), 128.7, 128.3, 116.2 (10C, 2Ar), 119.2 (q, ^1J 268, 2CF$_3$), 112.3 (2C-4), 29.3 (2CH$_2$). Anal. Calc. for $C_{24}H_{14}F_8N_4O_2$ (542.10): C, 53.15; H, 2.60; N, 10.33%. Found: C, 53.34; H, 2.86; N, 10.03%.

*Synthesis of 1-[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutane hydrazides (**4c-d, 4g**)*

General procedure

To an ice-cold stirred mixture of 4-substituted 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1c-d** (10 mmol) diluted in ethanol (15 mL) another mixture of succinic acid dihydrazide (10 mmol) and ethanol (10 mL) was added at room temperature. The resulting new mixture was stirred for 4 h at 50 ºC. After the reaction time the solvent was evaporated to half by rotatory evaporator under reduced pressure and after cooling (≤ 8 ºC) for 1-2 days the compounds **4c-d**, **4g** were obtained pure directly by filtration, washed with cold ethanol and dried under vacuum apparatus.

*1-[5-(Trifluoromethyl)-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutane hydrazide (**4c**)*

Yield 81%, mp 240-241 ºC. ^{1}H NMR: δ 8.97 (s, 1H, NH), 8.01 (s, OH), 7.79-7.82 (m, 2H, Ar), 7.48-7.50 (m, 3H, Ar), 4.16 (s, 2H, NH$_2$), 3.9 (d, 1H, H-4, *J* 19), 3.55 (d, 1H, H-4, *J* 19), 3.07 (s, 2H, CH$_2$), 2.24 (s, 2H, CH$_2$). ^{13}C NMR: δ 170.7 (C=O), 170.1 (C=O), 151.4 (C-3), 128.2, 127.8, 122.6, 114.2 (4C, Ar), 122.7 (q, ^1J 289, CF$_3$), 90.8 (q, ^2J 34, C-5), 44.4 (C-4), 29.3 (CH$_2$), 28.9 (CH$_2$). Anal. Calc. for $C_{14}H_{15}F_3N_4O_3$ (344.11): C, 48.84; H, 4.39; N, 16.27%. Found: C, 48.5; H, 4.01; N, 16.34%.

*1-[5-(Trifluoromethyl)-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutane hydrazide (**4d**)*

Yield 77%, mp 194-195 ºC. ^{1}H NMR: δ 8.98 (s, 1H, NH), 7.94 (s, OH), 7.74 (d, 2H, Ar), 7.00 (d, 2H, Ar), 4.15 (s, 2H, NH_2), 3.85 (d, 1H, H-4, *J* 19), 3.51 (d, 1H, H-4, *J* 19), 3.81 (s, 3H, OMe), 3.04 (s, 2H, CH_2), 2.24 (s, 2H, CH_2). ^{13}C NMR: δ 174.7 (C=O), 170.0 (C=O), 150.9 (C-3), 161.0, 130.1, 122.5, 114.9 (4C, Ar), 125.7 (q, ^1J 284, CF_3), 90.7 (q, ^2J 32, C-5), 55.1 (OCH_3), 44.2 (C-4), 29.3 (CH_2), 26.0 (CH_2). Anal. Calc. for $C_{15}H_{17}F_3N_4O_4$ (374.12): C, 48.13; H, 4.58; N, 14.97%. Found: C, 48.29; H, 4.51; N, 14.73%.

*1-[5-(Trifluoromethyl)-5-hydroxy-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]-4-oxobutane hydrazide (**4g**)*

Yield 52%, mp 239-240 ºC. ^{1}H NMR: δ 8.96 (s, 1H, NH), 8.30-8.33 (d, 2H, Ar), 8.05-8.07 (m, 2H, Ar), 4.15 (s, 2H, NH_2), 4.06 (d, 1H, H-4, *J* 19), 3.63 (d, 1H, H-4, *J* 19), 3.12 (s, 2H, CH_2), 2.24 (s, 2H, CH_2). ^{13}C NMR: δ 170.7 (C=O), 170.2 (C=O), 149.8 (C-3), 148.1, 136.2, 127.9, 127.3 (4C, Ar), 122.4 (q, ^1J 289, CF_3), 91.5 (q, ^2J 32, C-5), 44.1 (C-4), 29.3 (CH_2), 28.9 (CH_2). Anal. Calc. for $C_{14}H_{14}F_3N_4O_5$ (389.09): C, 43.19; H, 3.62; N, 17.99%. Found: C, 43.24; H, 3.61; N, 18.03%.

*Synthesis of 1-[5-(trifluoromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]-4-[5-(trichloromethyl)-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-diones (**5b**-**c**)*

General procedure

A stirred solution of 1-(4,5-dihydro-1*H*-pyrazol-1-yl]-4-oxobutane hydrazides (**4b-c**), 4-substituted 4-methoxy-1,1,1-trichloroalk-3-en-2-ones and ethanol (20 mL) was heated at 50 ºC for 16 h. After the reaction time the solvent was evaporated to half by rotatory evaporator under reduced pressure and after cooling (≤ 8 ºC) for 1-2 days the compounds **5b**-**c** were obtained pure directly by filtration, washed with cold ethanol and dried under vacuum apparatus.

*1-[5-(Trifluoromethyl)-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-4-[5-(trichloromethyl)-5-hydroxy-3-methyl-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**5b**)*

Yield 91%, mp 205-206 ºC. ^{1}H NMR: δ 8.05 (s, 1H, OH'), 7.72 (s, 1H, OH), 7.79-7.82 (m, 2H, Ar), 7.48-7.50 (m, 3H, Ar), 3.90 (d, *J* 19, 1H, H-4'), 3.55 (d, *J* 19 1H, H-4'), 3.50 (d, *J* 19, 1H, H-4), 3.34 (d, *J* 19, 1H, H-4), 3.07 (s, 2H, CH_2'), 2.87 (s, 2H, CH_2), 2.12 (s, 3H, CH_3). ^{13}C NMR: δ 173.3 (C=O'), 170.2 (C=O), 151.3 (C-3'), 146.0 (C-3), 128.8, 128.6, 126.4, 126.3 (6C, Ar), 103.4 (CCl_3), 101.6 (C-5'), 122.5 (q, ^1J 290, CF_3), 91.1 (q, ^2J 34, C-5), 46.6 (C-4'), 44.2 (C-4), 29.4 (CH_3), 28.7 (CH_2'), 28.1 (CH_2). Anal. Calc. for $C_{19}H_{18}Cl_3F_3N_4O_4$ (374.12): C, 43.08; H, 3.42; N, 10.58%. Found: C, 43.41; H, 3.85; N, 10.75%.

*1-[5-(Trifluoromethyl)-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-4-[5-(trichloromethyl)-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]butane-1,4-dione (**5c**)*

Yield 75%, mp 214-215 ºC. ^{1}H NMR: δ 7.99 (s, 1H, OH'), 7.92 (s, 1H, OH), 7.79-7.83 (m, 4H, Ar), 7.48-7.49 (m, 6H, Ar), 3.98 (d, *J* 19, 1H, H-4'), 3.89 (d, *J* 19, 1H, H-4), 3.78 (d, *J* 19, 1H, H-4'), 3.56 (d, *J* 19, 1H, H-4), 3.11 (s, 2H, CH_2'), 3.07 (s, 2H, CH_2). ^{13}C NMR: δ 172.5 (C=O'), 170.0 (C=O), 153.5 (C-3'), 151.1 (C-3), 130.5, 130.2, 129.7, 129.3, 128.5, 128.4, 126.3, 126.2 (12C, 2Ar), 103.3 (CCl_3), 101.4 (C-5'), 125.6 (q, ^1J 285, CF_3), 90.9 (q, ^2J 34, C-5), 46.5 (C-4'), 44.1 (C-4), 29.7 (CH_2'), 29.2 (CH_2). Anal. Calc. for $C_{24}H_{20}Cl_3F_3N_4O_4$ (590.05): C, 48.71; H, 3.41; N, 9.47%. Found: C, 49.11; H, 3.74; N, 9.42%.

Acknowledgments

The authors are thankful for the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq (Proc. No. 303296/2008-9). Fellowships from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES (Cechinel, C. A.) and CNPq (Porte, L. M. F.) are also acknowledged.

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Submitted: February 9, 2010
Published online: May 20, 2010